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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
BASI, NIRMAL SINGH	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/909,088	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	NIRMAL S. BASI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-47,49-52 and 55-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-47,49-52 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Upon further review the finality of the previous office action is withdrawn. The claims are newly rejected for the reason given below. In view of the appeal brief filed on 1/3/08, PROSECUTION IS HEREBY REOPENED.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

2. The rejection under 35 USC § 101 for lack of utility is withdrawn in view of applicants arguments filed 1/3/08. Applicants' arguments, pertaining to the rejection of claims 39-47, 49-52, 55-58 under, 35 U.S.C. 112, first paragraph, as lacking enablement, have been fully considered but they have not been found to be persuasive. Applicants' arguments are discussed in the rejection below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 39-47, 49-52, 55-58 are rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for reasons of record and those given below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue compounds which stimulate the proliferation of stimulated T-lymphocytes are useful therapeutically where the enhancement of an immune response would be beneficial. However, the ability of the claimed PRO335 to stimulate or inhibit lymphocyte proliferation in the MLR assay does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function for a therapeutic suppression of the immune system. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not enabled by the disclosure of the instant specification. The only use contemplated for the claimed invention is a therapeutic suppression of the immune system. Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result *in vitro* does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element

Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. Therefore, while the art recognizes the MLR assay as accepted for initial screening for immunosuppressive or immunostimulative molecules in vitro, which is not art recognized for being generally predictive of their in vivo effectiveness, this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes.

The enablement of claimed invention is based on Assay 74 disclosed in the specification. Assay 74 states, "Positive increases over control are considered positive with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein." Applicants further look for support in the declaration of Sherman Fong. Dr. Fong generally discusses that the MLR assay is widely used and discloses IL-22 as a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay. Dr. Fong further goes on to state on page 3, paragraph 10, "It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by Il-2". The examiner agrees with the statement that that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with at least 180% of the control, as specified in the present application, could possibly have the type of activity as that exhibited by Il-2. The problem is that PRO335 has not been disclosed to have T-cell proliferation activity in the MLR assay with at least 180% of the control. The exact value is not disclosed. The number of samples tested is not disclosed. The statistical analysis applied to analyze the results is not disclosed. The disclosure only states that the results were positive. A result of 100.1% is positive; just as a result of 180% is positive. Lets turn to assay 79, which is similar to assay 74, but where any decrease is considered to

be a positive result for an inhibitory compound, with decreases of less than or equal to 80% being preferred. Based on the prior art and even Applicants preferences, values around the control are less preferable, because clear statements such as those by Dr. Fong that the MLR assay of the present invention with at least 180% of the control could possibly have the type of activity as that exhibited by Il-2 could not be made otherwise. Could this statement be made if the activity was 100.1%, for example? The specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay. The specification provides no information at all regarding the results of the assay except that certain proteins tested positive and the statement that "any value greater than control indicates a stimulatory effect for the test protein". The magnitude of the value over control is important, even Dr. Fong highlights the value of 180%.

The questions are: What specific disease states would benefit by therapeutic enhancement of stimulation of lymphocyte proliferation by use of the claimed PRO335? What do the results of the MLR assay of Example 74, using PRO335, disclose about the disease state that could be treated by stimulation of lymphocyte proliferation? As disclosed by the examples provided by applicant different compounds effect the stimulation of lymphocyte proliferation to different degrees and in turn have different therapeutic effects. Il-2 arguments natural killer cell activity in patients with AIDS and is recommended for advanced renal cell carcinoma. Il-15 which was found to be at least as potent and effective as IL-2 in the MLR assay prolongs survival of lymphoma-bearing mice and suppresses pulmonary metastases induced by injection of sarcoma. Il-21 found to enhance the proliferation of T cells in an MLR assay potentially inhibits B16 melanoma tumors. Alpha-GalCer demonstrated to enhance the T-cell response in an MLR assay inhibits tumor metastasis in liver or lung. Therefore, based on the varied effects of the compounds that have stimulated the lymphocyte proliferation assay no prediction as to the specific therapeutic value of PRO335 cannot be made

without further experimentation. The compounds that tested positive in the MLR assays discussed above did not produce the same amount of stimulation in the assays and did not result as therapeutics for the same disease states.

The MLR assay is an accepted preliminary *in vitro* model for screening immunosuppressive or immunostimulant agents. However, the assay must be evaluated as it pertains to the asserted use of the claimed invention, which is for therapeutic enhancement of the immune response of an individual. If the claimed invention is to be used for therapeutic enhancement of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted use of the claimed invention? Fung-Leung et al. cited by Applicants (see IDS) for support that the MLR assay is used for identifying immunomodulatory compounds. However, the disclosure of Fung-Leung et al. is much more than what is in the instant specification and the immunosuppressive effect being measured was specifically for alloantigens. Several controls were run, as were determinations that the inhibitory effect was not related to cell toxicity. Lastly, Fung-Leung et al. concluded that the results of the multiple MLR assays and controls "suggests its potential use as an immunosuppressant in clinical therapy" (page 364, first sentence). It was not until the compound was tested in an *in vivo* mouse model that the authors declared it an immunosuppressant. Therefore, the conclusions reached by Fung-Leung et al. are based on much more experimental data, assays and testing that that provided in the instant specification and the reference does not support the position that the MLR assay in the instant specification is predictive of use as a therapeutic compound for suppressing the immune response. The results of the MLR assay in the instant specification are merely preliminary, and much more experimentation is necessary for one of ordinary skill in the art to use the claimed invention in the manner disclosed. This experimentation would be considered undue, because until it is performed, the skilled artisan cannot use the claimed invention in the manner disclosed.

Further, there is no guidance in the specification as to how PRO335 could be used to boost the response to any antigen. Current Protocols in Immunology states on p. 3.12.11 that the MLR "only detects dividing cells instead of measuring true effector T-cell function" and that it is "not clear which T cell function is measured in proliferate assays", and further that "the proliferate response should be used solely as a general indicators of T cell reactivity". Data obtained might variously reflect proliferation of CTL, lymphokine producing T cells, or non-activated bystander cells and will be severely affected by the function of non-T cells. Differences in responsiveness in a proliferative assay in part reflect differences in IL-2 production, according to Current Protocols in Immunology. As has been stated previously, the MLR measures the reactivity of one individual to another and is, as Current Protocols in Immunology states, **highly variable**. Current Protocols in Immunology in fact describes many variables that must be controlled for. In the instant application, no such controls, such as for maximum response or for the inherent variability of individual responses, are provided. There is no indication of the statistical significance of the results. There are no autologous controls. No correlation is provided to any particular *in vivo* function; there is no guidance to indicate that PRO335 could be used to any therapeutic effect for the treatment of diseases such as cancer or HIV. The references cited by Applicant fail to provide compensatory guidance. Steinman and Thurner et al. (cited by applicants on 8/20/04) address the utility of dendritic cells but not of a stimulatory MLR. Gubler (cited by applicants on 8/20/04) describes the identification of the molecule IL-12 but uses the MLR merely to compare activities, not as the basis for describing a molecule as a therapeutically useful immunostimulant. The subsequent research of Peterson et al. (cited by applicants) was clearly required to suggest that the molecule could be used in this fashion. Thus, without further guidance correlating the observed stimulatory activity to a particular, useful property, it would require undue experimentation to use PRO335 .

Further many of the nucleic acids that hybridize to the nucleic acids (a)-(f) of claim 52 will encode non functional polypeptides or encode proteins completely functionally unrelated to PRO335. The specification does not disclose how to use said nucleic acids.

Returning to the Declaration of Dr. Sherman Fong. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, and the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not the disclosure that PRO335 tested "positive" in the MLR assay of Example 74 supports the assertion that it could be used to stimulate proliferation of T-lymphocytes. Dr. Fong's statement that the present invention has an activity of at least 180% is questioned because there is no data presented to support this conclusion. The specification may state that increases of greater than or equal to 180% are preferred, but there is no disclosure, in the specification or in any other source, that the alleged increase reported in the specification for the claimed protein was of any particular degree. The only conclusion that can be made from the evidence provided for the claimed protein of PRO 335 is that the increase was a value greater than control since this was the standard provided for determination of a positive increase. Without the knowledge of the exact magnitude of the increase over control the significance of the result can be evaluated so as to provide enablement of the claimed invention in any specific *in vivo* therapeutic use. The expert has interest in the outcome of the case since Dr. Fong is listed as an inventor and is employed by the assignee. Finally, the expert refers to Gubler et al. as factual support for the conclusions in the declaration. Guber discloses the effect of IL-12 which was determined by more

research following the MLR assay. However, Gubler does not appear to indicate that all proteins shown to be positive in an MLR assay would be expected to have the same effects on the same disease states as those shown by IL-12. Further, Gubler et al. (as well as Peterson et al. and Thurner et al.) are silent to any activity possessed by the PRO 335 as it pertains to its *in vivo* use. The Fong declaration evinces that the instant specification provides a mere invitation to experiment, and not how to use the invention. Also, it is noted that no agonistic or antagonistic effect of molecules on PRO335, as it relates to its effect on a specific disease state, are disclosed in the specification. Also, no molecules that specially bind to PRO335 were evaluated in the MLR assay. Because the claimed invention is not enabled and does not meet the requirements of 112/1st paragraph for the reasons provided above and the previous office actions.

4. Claims 39-43, 52 and 55-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant ad that the inventors), at the time the application was filed, had possession of the claimed invention. The claims are drawn to nucleic acid (polynucleotides) having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence, or capable of hybridizing to a particular disclosed sequence. The claims do not require that the polynucleotide or encoded polypeptide possess a specific function associated with PRO335, only that the polypeptide encoded by said polynucleotide be immunostimulant. All polypeptides can be considered immunostimulants. All polypeptides can be considered immunostimulants since they can produce antibodies. Applicants argue that only polypeptides that show a positive hit in the MLR assay as immunostimulants are the only variants encompassed by the claims. Applicants' arguments have been fully considered but they are not found persuasive. The claims, as written, are not limited to

polypeptides that show a positive hit in the MLR assay, they encompass all immunostimulat activities. The question is which specific variants of PRO355 will show a positive hit in the MLR assay. Although, the structure of all PRO355 variants can be envisioned, no prediction, based on the structure PRO355 variants, can be made as to which of these variants show a positive hit in the MLR assay. The structure of PRO355 which causes a positive hit in the MLR assay is not disclosed. To be more specific, apart from the polynucleotide of SEQ ID NO:289 encoding the polypeptide of SEQ ID NO:290, the particular conserved structures or other distinguishing structural features critical for a specific activity of PRO 335 are not disclosed. Thus, the claims are drawn to genus of polypeptides that is defined only by sequence identity and general immunostimulat activity (applicable to many other polypeptides) and no specific activity that can be associated with any specific domains of PRO335 that would cause it to result in a positive hit in the MLR assay.

Applicants argue and state, "the specification shows that Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teachings provided by the specification. The inventor is not required to describe every single detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains." Applicants further argue that structure and function of the claimed variants can be determined based on the specification. Applicants' arguments have been fully considered but they are not found persuasive. Apart from the polynucleotide of SEQ ID NO:289 encoding the polypeptide of 290, the particular conserved structures or other distinguishing structural features critical for a specific activity of PRO 335 are not disclosed. Thus, the claims are drawn to genus of polynucleotides that is defined only by sequence identity and general activity (applicable to many other polynucleotides) and no specific activity that can be associated with any specific domains of PRO335.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all nucleic acid that achieves a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. The claims recite a broad arbitrary structural relationship between the claimed nucleic acid sequences, either in terms of its nucleotide sequence or the polypeptide encoded, and the single disclosed species of nucleotide sequence and amino acid sequence, respectively. The claims are not even directed to polynucleotides, which encode a specific function associated with PRO335, only a general function associated with all proteins. Further, if applicant argues PRO335 works in the MLR assay by immumostimulation, it must be noted that the immunostimulation activity is not considered an activity that that has been correlated with a specific structure contained in PRO335 as it pertains to said assay. Further, nucleic acids encoding non-functional or functionally unrelated proteins to PRO335 are encompassed by the claims. The recited structural

relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to the recited nucleotide sequence or that encodes a polypeptide that is not 100% identical to the recited amino acid sequence.

While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specific activity of the protein of SEQ ID NO:290. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a functional polypeptide than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}) . The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}. For a 300 nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6×10^{56}.

In the present case, the reference amino acid sequence, SEQ ID NO:290, is 1059 amino acids long, and the reference nucleotide sequence, SEQ ID NO:289 is 3662 nucleotides long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least e.g. 80% identical to the reference amino acid sequence or nucleotide sequence, would be much larger than 6×10^{23} and 1.6×10^{56}, respectively. While limiting the scope of potential sequences to those that are at least e.g. 80% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. All of these values greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the

recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those, which encode a functional protein encompassed by the claims. Therefore, inclusion of the structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.*

The specification does not provide any information on what amino acid residues are necessary and sufficient for a functional activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in an active PRO335 polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of proteins that have structural homology with SEQ ID NO:335 to predict function or functional domains required for activity, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Therefore one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in case to case painstaking experimental study to determine active PRO335 variants. Consequently, excessive trial and error experimentation would have been required to identify the biologically active derivatives of PRO335 with an amino acid sequence differing from SEQ ID NO:290 since the amino acid sequence of such polypeptides could not be predicted.

The specification discloses only one putative amino acid sequences, SEQ ID NO:290, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining functional polypeptide variants of SEQ ID NO:290 encoded by the nucleic acid of SEQ ID NO:289 which would be suitable.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 , clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for

purposes of the 'written description" inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the ad to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Further many of the nucleic acids that hybridize to the nucleic acids (a)-(f) of claim 52 will encode non functional polypeptides or encode proteins completely functionally unrelated to PRO335. The hybridization conditions do not select for function. In addition hybridization conditions do not predict function or even select for nucleic acid encoding functional protein

Therefore, only isolated nucleic acid encoding the polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 290 but not the full breadth of the claims meet the written description provision of 35 U.S.C.112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1 115).

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIRMAL S. BASI whose telephone number is (571)272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nirmal S. Basi/
Examiner, Art Unit 1646

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646